IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of

PEPYS

Application No.: 09/737,544

Filed: December 18, 2000

Title: TREATMENT AND PREVENTION OF TISSUE DAMAGE

Group Art Unit: 1617

Confirmation No.: 1521

Examiner: Shengjun WANG

DECLARATION BY PROFESSOR MARK B. PEPYS PURSUANT TO 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Mark B. Pepys, hereby declare as follows:

(1) I am Professor of Medicine and Head, Department of Medicine, Hampstead Campus, Royal Free and University College Medical School, London, U.K. Further details of my educational qualifications and a list of publications are set out on the attached curriculum vitae (see Appendix A).

(2) I have worked in the field of chemical, biological, and clinical investigation of C-reactive protein (CRP) for 30 years.

(3) I am the sole inventor of U.S. Patent Application No. 09/737,544, entitled "Treatment and Prevention of Tissue Damage" ("the '544 application").

(4) I have invented a method for selecting a pharmaceutical for treating or preventing CRP-mediated tissue damage in a subject comprising identifying and selecting a compound that inhibits the binding of CRP to an autologous or extrinsic ligand thereof, and a method for treating or preventing C-reactive protein (CRP)-mediated tissue damage comprising administering to a subject in need thereof an effective amount of a compound capable of inhibiting the binding of CRP to an

autologous or extrinsic ligand thereof. Original claims 1-25 and 39-48 of the '544 application that were elected for examination are directed to embodiments of my invention pertaining to a method for treating or preventing CRP-mediated tissue damage a subject in need thereof comprising administering to the subject an effective amount of phosphocholine or a derivative thereof that inhibits the binding of CRP to an autologous or extrinsic ligand thereof.

(4) I have read and am familiar with the official action issued by the U.S. Patent and Trademark Office and dated September 2, 2005, in connection with the '544 application.

(5) I make this declaration in response to the official action issued September 2, 2005, in which claim 1 was rejected under 35 U.S.C. §112, first paragraph, because the specification is considered to enable one of skill in the art to treat atherosclerosis, but is not considered to provide enablement for preventing atherosclerosis or for treating or preventing tissue damage in general.

(6) The examiner alleges that the term "tissue damaging condition" as used in the application includes all disorders, and argues that the specification is inadequate because it does not teach a method for treating and/or preventing all disorders. I strongly disagree with the examiner's allegation that the term "tissue damaging condition" as used in the '544 application includes all disorders. As amended by the response submitted herewith, claim 1 identifies a selected set of conditions associated with tissue damage accompanied by an elevated level of CRP, for which the claimed method will operate successfully to treat or prevent CRP-mediated tissue damage. In particular, claim 1 clearly specifies that the tissue damage that is treated or prevented by the claimed method is associated with a condition selected from the group consisting of an infection, an allergic complication of infection, an inflammatory disease, ischemic or other necrosis, traumatic tissue damage and malignant neoplasia. The application provides a sound and compelling scientific basis for the breadth of the present claims. All of the information needed by a person of skill in the art to practice the claimed method successfully may be found in the application.

(7) As discussed in the '544 application, CRP-mediated tissue damage that can be treated and/or prevented successfully by the claimed invention includes the tissue damage associated with heart attacks and strokes. Complement mediated inflammation exacerbates the tissue injury of ischemic necrosis in heart attacks and strokes, the most common causes of death in developed countries. Large infarct size increases immediate morbidity and mortality and, in survivors of the acute event, larger non-functional scars adversely affect long term prognosis. There is thus an important unmet medical need for new cardioprotective and neuroprotective treatments. The experimental results described herein further demonstrate the operability of the claimed invention, and are additional evidence that a person of skill in the art can practice the claimed invention successfully without having to perform undue experimentation.

(8) I have previously shown that human C-reactive protein (CRP), the classical acute phase protein that binds to ligands exposed in damaged tissue and then activates complement, increases myocardial and cerebral infarct size in rats subjected to coronary or cerebral artery ligation respectively. Rat CRP does not activate rat complement whereas human CRP activates both rat and human complement, and administration of human CRP to rats is thus considered to be an excellent model for actions of endogenous human CRP. Here I describe results obtained upon administering a phosphocholine derivative 1,6-bis(phosphocholine)-hexane, referred to as bis(PC)-H that binds to CRP and inhibits the binding of CRP to its ligands, to rats undergoing acute myocardial infarction. The administration of bis(PC)-H completely abrogates the greatly increased infarct size and cardiac dysfunction produced by injection of human CRP. Therapeutic inhibition of CRP is thus a promising new approach to cardioprotection in acute myocardial infarction. Other therapeutic applications of the method of administering a phosphocholine derivative that binds to CRP and inhibits the binding of CRP to its ligands include neuroprotection in stroke, and the many other inflammatory, infective and tissue damaging conditions characterized by increased CRP production, in which binding of CRP to ligands exposed in damaged cells may lead to complement mediated exacerbation of tissue injury.

(9) **Methods**

Reagents and assays. Human CRP was isolated from malignant ascites fluid as described previously. Human CRP was assayed by the Roche and Dade-Behring methods, and by electroimmunoassay. Rat CRP and C3 were measured by electroimmunoassay. Calcium dependent binding of ^{125}I-labelled CRP to pneumococcal C-polysaccharide (Statens Serum Institut, Copenhagen, Denmark) and modified human low density lipoprotein, which were covalently immobilized on Corning Costar N-hydroxysuccinimide microtitre plates, was compared in the presence and absence of inhibitor compounds. Binding of CRP to phosphoethanolamine-Sepharose was determined as reported previously for SAP. Activation of complement in whole human serum by CRP and C-polysaccharide in the presence and absence of bis(PC)-H was monitored by 2D immunolectrophoresis with monospecific antiserum to human C3. Binding affinity of CRP for ligands in solution in 0.01M Tris, 0.14M NaCl, 0.002M $CaCl_2$, 0.1% NaN_3, pH 8.0 (TC buffer plus azide) was measured at 37°C by isothermal titration calorimetry. Effects of bis(PC)-H on CRP molecules were monitored by chromatography on a Superdex™ 200 HR10/30 column in the AKTA™ Explorer 100 HPLC system (Amersham Biosciences) eluted with TC buffer, by uranyl acetate negative staining electron microscopy on carbon grids, and by electrospray mass spectrometry.

Myocardial infarction. ALZET® osmotic mini-pumps, delivering 10 µl/h for 7 d, were implanted subcutaneously in male Wistar rats (200-220 g) 2 d before coronary artery ligation. Groups A and B received TC buffer; group C received 1.0 M bis(PC)-H in TC buffer, providing 1 mmol/kg/day. Coronary artery ligation, or sham-operation, were performed under intraperitoneal anesthesia with 75 mg/kg ketamine, 0.6 mg/kg xylazine and 0.2 mg/kg atropine and post-operative atipamezole 0.5 mg/kg 2 d after pump implantation. Five daily subcutaneous injections of either TC buffer alone (group A) or human CRP at 40 mg/kg/day in TC buffer (groups B and C) were given, starting immediately after recovery from coronary surgery. Echocardiography (10-22 MHz probe, Dynamic Imaging, Livingston, UK), right carotid artery cannulation using a pressure-transducer tipped catheter (1.4F, Millar Instrument Inc, USA) and cardiac

catheterization were performed on day 5 under isofluorane anesthesia. The rats were then bled, hearts excised, cleaned, weighed and frozen. Frozen hearts were cut transversely into 2.5 mm slices and stained with 1% w/v 2,3,5-triphenyl tetrazolium chloride in phosphate buffer. Infarct size was measured by planimetry (MCID image analysis system, Imaging Research Inc.) on formalin fixed glass mounted sections, and confirmed by dissection and weighing. All treatments and measurements were blinded.

(10) **Results**

Bolus intravenous or intraperitoneal injections in mice and rats of up to 1 mmol/kg of bis(PC)-H in physiological saline solution, or continuous infusion at 1 mmol/kg/day for 7 days via subcutaneous osmotic pump, were tolerated without noticeable adverse effects, and inhibited binding of injected human CRP to other ligands and its reactivity in the Roche assay. The plasma half life was ~90 minutes in mice. Continuous infusion of 1 mmol/kg/day of bis(PC)-H in rats completely blocked daily subcutaneous injections of 40 mg/kg of human CRP (~1.74 μmol CRP protomer) despite the presence of rat CRP which circulates at 300-500 mg/l, is produced at the rate of ~10 μmol protomer/kg/day and bound the drug with K_d ~ 150 nM.

Clinical treatment with a CRP inhibitor drug would be started immediately on admission to hospital following an acute myocardial infarction, thus preceding the acute phase CRP response, which starts about 6 h after onset of pain and peaks at about 50 h. We therefore initiated infusion of bis(PC)-H before coronary artery ligation in rats, and gave the first of five daily subcutaneous injections of human CRP immediately after recovery from surgery, closely replicating the initial dynamics of the endogenous human CRP response. Administration of human CRP was associated with increased mortality compared to vehicle only controls. In contrast there were no deaths among the rats receiving bis(PC)-H in addition to CRP (Table 1) (Fisher's exact test for comparison of mortality in all groups, P=0.08). Infarct size on day 5 was substantially larger in the rats treated with CRP (unpaired t-test, P=0.0001), but in rats receiving bis(PC)-H as well as CRP, infarct size was the same as in the vehicle only controls (Table 1). Electro- and echocardiographic indices of

cardiac function on day 5 were consistent with the larger infarcts in the CRP treated rats and with the protective effect of bis(PC)-H (Table 1).

At bleed out on day 5, 24 h after the last dose of human CRP, the mean (SD) serum human CRP concentration in the CRP treated group was 16.7 (10.6) mg/l but human CRP was detectable in the sera of only 4 of the 11 CRP treated rats receiving bis(PC)-H, and at much lower concentration, mean (SD) 3.3 (1.5) mg/l, none of which was detectable by the Roche assay. Continuous infusion of bis(PC)-H thus caused accelerated clearance of human CRP as well as blocking its function.

Table 1. Enhancement of myocardial infarct size and cardiac dysfunction by human CRP is completely inhibited by 1,6-bis(phosphocholine)-hexane (bis(PC)-H) treatment

	Sham operated	Coronary artery ligation			P values		
Group (n), treatment	(5), none	A (12), vehicle	B (15), CRP	C (11), CRP + bis(PC)-H	A vs B	A vs C	B vs C
Infarct size (%, p)	0	17.0 (3.8)	24.8 (3.3)	18.6 (3.8)	0.0001	0.32	0.0002
Infarct size (%, w)	0	17.7 (4.7)	29.5 (5.7)	18.4 (3.7)	0.0001	0.68	0.0001
ST voltage (μV)	-44.8 (24.1)	14.9 (82.3)	95.0 (61.8)*	16.2 (74.3)	0.006	0.97	0.008
Elevated ST, n (%)	0	7 (58.3)	14 (100)*	7 (63.6)	0.007	1.00	0.06
Ejection fraction %	72.67 (3.91)	37.41 (15.95)	28.75 (14.82)	38.40 (11.47)	0.16	0.87	0.08
LVEDP (mm Hg)	4.4 (1.8)	8.8 (4.1)	12.9 (3.8)	4.2 (6.3)	0.01	0.05	0.0002
LVEDD (mm)	6.54 (0.24)	7.43 (0.87)	8.06 (0.74)	7.19 (1.08)	0.05	0.56	0.02
LVESD (mm)	3.1 (0.51)	5.94 (1.39)	6.70 (1.21)	5.60 (1.16)	0.14	0.53	0.03

Values shown are mean (SD). P values are from unpaired t-tests. Infarct size on day 5, % of left ventricle measured by planimetry (p) and by weight (w); ST, ST segment of the electrocardiogram; LVEDP, left ventricular end diastolic pressure; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; *, n = 14 for these measurements

(11) I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and may jeopardize the validity of the application or any patent issued thereon.

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MARK B. PEPYS

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Date

APPENDIX A

MARK BRIAN PEPYS

CURRICULUM VITAE

Name	MARK BRIAN PEPYS
Address	22 Wildwood Road, London NW11
Date of birth	18th September, 1944

Present appointment	Date of Appointment
Professor of Medicine and Head, Department of Medicine, Hampstead Campus, Royal Free and University College Medical School, University College London	01/10/99

MARK BRIAN PEPYS

University Education

Trinity College, Cambridge	1962-1965
University College Hospital Medical School	1965-1968

Degrees

B.A. (Hons.) (Cantab.)			1965
Natural Sciences Tripos:	Part I	Class I	
	Part II	Class I	
M.B., B.Chir. (Cantab.)			1968
M.A. (Cantab.)			1970
M.R.C.P. (U.K.)			1970
Ph.D. (Cantab.)	*"Role of complement in induction of the allergic response"*		1974
F.R.C.P.			1981
M.R.C.Path.			1981
M.D. (Cantab.)	*"Clinical and experimental studies of C-reactive protein and amyloid P component"*		1982
F.R.C.Path.			1991
F.R.S.			1998
F.Med.Sci.			1998

Academic distinctions

State Scholarship	1961

Trinity College, Cambridge:

Open Exhibition in Natural Sciences	1961
Preliminary Examination for Natural Sciences Tripos, Class I	1963
Preliminary Examination Prize	1963
Natural Sciences Tripos, Part I, Class I	1964
Senior Scholarship	1964
Natural Sciences Tripos, Part II (Pathology), Class I	1965
Tripos Examination Prize	1965
Research Scholarship	1970
Fellowship (Title A)	1973-1979

MARK BRIAN PEPYS

University College Hospital Medical School:

Filliter Entrance Scholarship in Pathology and Microbiology	1965
Trotter Medal for Clinical Surgery	1966
Alexander Bruce Gold Medal for Surgical Pathology	1967
Filliter Exhibition in Pathology and Microbiology	1967
Fellowes Gold Medal for Clinical Medicine	1967
Sir William Gowers Prize for Clinical Medicine	1967
Liston Gold Medal for Clinical Surgery	1967
Atchison Scholarship for "Clinical and Academic Attainment"	1968-1969

Royal College of Physicians:

Goulstonian lecturer *"C-reactive protein, amyloidosis and the acute phase response"*	1982
Lumleian lecturer *"C-reactive protein and amyloidosis: from proteins to drugs?"*	1998
Moxon Trust Medal	1999

Royal College of Pathologists:

Kohn lecturer *"Serum amyloid P component: molecular interactions and clinical applications"*	1991

Royal College of Surgeons of England:

Sir Arthur Sims Commonwealth Travelling Professorship	1991

Royal Society of London:

Fellow	1998

Academy of Medical Sciences:

Founder Fellow	1998

Renal Association:

Chandos lecturer *"Prognostic and pathogenetic significance of C-reactive protein"*	2000

MARK BRIAN PEPYS

British Society for Rheumatology:

Heberden medallist and orator
"Pentraxins in rheumatology: physiology, pathology and new drugs" 2002

University College London:

Fellow 2003

American Society of Nephrology:

State of the Art lecturer
"Recent advances in systemic amyloidosis" 2003

Israel Society for Rheumatology:

Gerald Loewi Memorial lecturer
"Amyloidosis and C-reactive protein: from old molecules to new drugs" 2004

Imperial College Faculty of Medicine:

Fellow 2004

Membership of Scientific and Medical Societies

Fellow of the Royal Society
Fellow of the Royal College of Physicians, London
Fellow of the Royal College of Pathologists
Founder Fellow of the Academy of Medical Sciences
Honorary Member of the Association of Physicians
Member Medical Research Society
British Society for Immunology
British Society for Allergy and Clinical Immunology
International Society for Amyloidosis
Antibody Club
Biochemical Society
British Society for Rheumatology
Molecular Medicine Society (Fellow)
Society for Neuroscience
American Association for the Advancement of Science
British Association

MARK BRIAN PEPYS

Membership of Academic Committees

University Grants Committee Equipment Sub-Committee	1989
Medical Research Council Systems Board Grants Committee B	1986-1990
Royal College of Physicians Specialist Committee on Clinical Immunology and Allergy	1988-1991
Royal Society Grants Committee F	1998-2001
Royal Society Sectional Committee 10	2001-2003
Medical Research Council Molecular and Cell Medicine Board	2000-2004
Royal Society Council	2003-2005
Academy of Medical Sciences Council	2004-2006

Membership of Editorial Boards

Journal of Immunological Methods	1975-1982
Clinical and Experimental Immunology	1980-1997
Clinical Allergy	1984-1988
Biochemical Journal, Editorial Adviser	1991-1998
Amyloid: Journal of Protein Folding Disorders	1994-

Previous appointments

House Physician to Medical Unit, University College Hospital, (Professor Lord Rosenheim, Professor C.E. Dent, FRS and Dr C.J. Dickinson)	1968-1969
House Surgeon to Surgical Unit, University College Hospital	1969
Senior House Officer to Dr D.K. Peters, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital	1969-1970
Research Assistant to Dr D.K. Peters, Honorary Medical Registrar, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital	1970
M.R.C. Junior Research Fellowship, Immunology Division (Professor R.R.A. Coombs, FRS), Department of Pathology, University of Cambridge	1970-1973
Research Scholar, Trinity College, Cambridge	1970-1973
Fellow, Trinity College, Cambridge	1973-1979
Medical Registrar to Professor C.C. Booth, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital	1973-1974

MARK BRIAN PEPYS

Previous appointments (cont)

Assistant Lecturer in Medicine, Honorary Senior Registrar to Professor C.C. Booth, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital	1974-1976
Senior Lecturer and Head of Immunology, Honorary Consultant, Royal Free Hospital School of Medicine	1976-1977
Senior Lecturer in Medicine, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital	1977-1980
Consultant Physician, Hammersmith Hospital, London	1977-1999
Reader in Immunological Medicine, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital	1980-1984
Group Leader, MRC Acute Phase Protein Research Group	1983-1988
Professor of Immunological Medicine, Department of Medicine, Royal Postgraduate Medical School, London	1984-1999
Assistant Director (Research), Department of Medicine, Royal Postgraduate Medical School, London	1987-1989
Research Coordinator to Hammersmith and Queen Charlotte's Special Health Authority	1988-1995

Research grants awarded

1975	Medical Research Council. *"Role of lymphocytes and complement in immunological function of the intestine"* £40,000 over 4 years
1977	Medical Research Council. *"Identification and absolute enumeration of lymphocyte populations in whole blood and tissue sections"* £33,000 over 3 years
1977	Medical Research Council. *"Role of complement in the induction of antibody formation in human and murine systems"* £33,000 over 3 years
1977	Medical Research Council. *"Immunological mechanisms underlying the acute and chronic relapsing forms of experimental allergic neuritis"* £34,000 over 3 years (with Professor P.K. Thomas)

MARK BRIAN PEPYS

Research grants awarded (cont)

1977 Wellcome Trust. *"Investigation of possible immunological factor in epilepsy"*
£20,000 over 2 years (with Professor G. Ettlinger)

1978 Wellcome Trust. *"Role of C-reactive protein in immunological responses"*
£25,000 over 3 years

1978 National Kidney Research Fund. *"C-reactive and amyloid P proteins in renal disease"*
£15,000 over 2 years

1979 Medical Research Council. Programme Grant. *"Biological and clinical studies of C-reactive protein and serum amyloid P component"*
£240,000 over 5 years

1979 Fisons Limited. *"Therapeutic trial of absorbable cromone in Crohn's disease"*
£17,000 over 2 years (with Dr V.S. Chadwick)

1980 Leukaemia Research Fund. *"Characterisation by surface markers and enumeration of leukaemic cells in whole blood using monoclonal antibodies and alkaline phosphatase labelled reagents: a method for routine clinical use"*
£35,000 over 3 years

1981 Medical Research Council
Training Fellowship for Dr I.F. Rowe
£30,000 over 3 years

1981 Cancer Research Campaign. *"Role of the interaction between fibronectin and amyloid P component in cell-substratum interactions of normal and malignant cells"*
£25,000 over 2 years

1982 Medical Research Council
Training Fellowship for Dr C.R.K. Hind
£33,000 over 3 years

1983 Medical Research Council. Programme Grant. Renewed for 1984-1989
£302,000 over 5 years

MARK BRIAN PEPYS

Research grants awarded (cont)

1983 Medical Research Council. Group status awarded and designated as the MRC Acute Phase Protein Research Group
£78,315 over 5 years

1986 Medical Research Council
Training Fellowship for Dr P.N. Hawkins
£45,000 over 3 years

1986 Medical Research Council. *"The three-dimensional structure analysis of pentraxins: biochemical and X-ray studies of serum amyloid P component"*
£52,000 over 3 years (with Dr S.P. Wood and Professor T.L. Blundell)

1987 Medical Research Council. *"$\beta_{\square}$-Microglobulin derived amyloidosis in haemodialysis and CAPD: precursor protein clearance and amyloidogenesis"*
£46,000 over 2 years (with Dr F.W. Ballardie and Professor D.N.S. Kerr)

1987 Medical Research Council. *"Structural studies of amyloid fibril proteins and their precursors"*
£44,000 over 3 years

1988 Arthritis and Rheumatism Council. *"Molecular, biological and clinical studies of pentraxin-chromatin interactions"*
£52,680 over 3 years

1989 Medical Research Council. *"Characterisation of amyloid fibril-associated glycosaminoglycans"*
£19,922 over 1 year

1989 Wellcome Trust. *"Localisation of serum amyloid P component in joints in vivo: mechanisms and significance"*
£96,500 over 2 years

1989 Medical Research Council. Programme Grant. *"Structural, functional and clinical studies of the pentraxins and amyloidosis"*
Renewed for 1989-1994
£532,600 over 5 years

MARK BRIAN PEPYS

Research grants awarded (cont)

1989 Medical Research Council. *"Three dimensional structure analysis of pentraxins: X-ray studies of ligand binding to serum amyloid P component"*
£87,300 over 3 years (with Professor T.L. Blundell and Dr S.P. Wood)

1989 Horserace Betting Levy Board. *"Development of an equine acute phase protein test for diagnosis"*
£44,830 over 3 years

1990 Medical Research Council. *"In vivo distribution, clearance and metabolism of C-reactive protein in man in health and disease"*
£100,500 over 3 years (with Dr P.N. Hawkins)

1991 Medical Research Council. Supplement to Programme Grant. 1990-1994
£108,000 over 4 years

1991 Medical Research Council. *"Characterisation of apoA-I mutations and mechanisms of amyloidogenesis in familial systemic Ostertag-type amyloidosis"*
£75,000 over 2 years (with Dr A.K. Soutar and Dr P.N. Hawkins)

1991 The Maurice Wohl Charitable Foundation
£90,000 towards building of new laboratories

1993 Medical Research Council. *"Expression, structure and properties of the human lysozyme variants Thr56 and His67. A new model of amyloidogenesis"*
£90,613 over 2 years (with Dr A.K. Soutar)

1993 Medical Research Council
Training Fellowship for Dr L.B. Lovat
£82,500 over 3 years

1994 Wellcome Trust. *"Biomedical applications of mass spectrometry"*
£312,369 (with Dr G.W. Taylor, Professor D.S. Davies and Professor R.I. Lechler)

MARK BRIAN PEPYS

Research grants awarded (cont)

1994 Medical Research Council. Programme Grant. *"Structural, functional and clinical studies of the pentraxins and amyloidosis"*
Renewed for 1994-1999
£2,035,148 over 5 years (with Dr P.N. Hawkins)

1994 Medical Research Council. *"Structure and ligand binding of serum amyloid P component"*
£134,858 over 3 years (with Dr S.P. Wood and Dr I.J. Tickle)

1995 Arthritis and Rheumatism Council
Clinical Research Fellowship for Dr M.C.M. Bickerstaff
£119,717 over 3 years (with Professor M.J. Walport)

1996 Medical Research Council. Supplement to Programme Grant 1996-1999
£148,584 over 3 years (with Dr P.N. Hawkins)

1996 F. Hoffmann-La Roche Ltd. *"Studies of serum amyloid P component in amyloidosis"*
£302,000 for equipment

1996 The Wellcome Trust. University Award for Dr P.N. Hawkins
"Diagnostic, pathogenetic and therapeutic studies in amyloidosis"
£205,412 over 3 years

1996 The Maurice Wohl Charitable Foundation
£22,000 towards purchase of equipment

1997 The Wellcome Trust. *"Ligand recognition and structure-function relationships in human C-reactive protein"*
£166,030 over 3 years (with Dr S.P. Wood)

1997 F. Hoffmann-La Roche Ltd. *"Studies of serum amyloid P component in amyloidosis"*
£105,000 over 1 year

1998 Joint Medical Research Council and Department of Health Transmissible Spongiform Encephalopathies Initiative. *"Do scrapie and Creutzfeldt-Jakob disease develop normally in mice with targeted deletion of the serum amyloid P component gene?"*
£315,482 over 3 years (with Professor J. Collinge, Dr M.E. Bruce and Ms P.A. McBride)

MARK BRIAN PEPYS

Research grants awarded (cont)

1998 Medical Research Council
Clinical Training Fellowship for Dr M. Noursadeghi
£108,800 over 3 years (with Professor J. Cohen)

1999 The Wellcome Trust
Research Training Fellowship for Dr J.D. Gillmore
£151,974 over 3 years

1999 Medical Research Council. Programme Grant. *"Pentraxins and amyloidosis: Functions and clinical significance"*
Renewed for 1999-2004
£2,362,180 over 5 years (with Professor P.N. Hawkins)

2000 British Heart Foundation. *"The diagnostic and prognostic significance of inflammation and the possession of certain vascular and inflammatory polymorphisms in coronary in-stent restenosis"*
£131,592 over 2 years (with Dr K.M. Fox and Professor S. Humphries)

2000 Medical Research Council, Development Grant
"Structural analysis of ligand recognition and associated biological roles of pentraxins"
£227,474 over 3 years (with Professor S.P. Wood)

2000 Medical Research Council
Clinical Training Fellowship for Dr G.M. Hirschfield
£112,753 over 3 years

2001 Supplement and extension to Joint Medical Research Council and Department of Health Transmissible Spongiform Encephalopathies Initiative. *"Do scrapie and Creutzfeldt-Jakob disease develop normally in mice with targeted deletion of the serum amyloid P component gene?"*
£60,636 over 18 months (with Professor J. Collinge, Dr M.E. Bruce and Ms P.A. McBride)

2002 The Wolfson Foundation, Equipment Grant
"Molecules to medicines at the Royal Free"
£1,500,000 (with Dr J.J. Hsuan)

2004 British Heart Foundation
PhD Studentship for Ms H. Mikolajek
£68,208 over 3 years (with Professor S.P. Wood)

MARK BRIAN PEPYS

Research grants awarded (cont)

2004 Medical Research Council. Programme Grant. *"Pentraxins and amyloidosis: From molecular mechanisms to medicines"*
Renewed for 2004-2009
£1,800,016 over 5 years (with Professor P.N. Hawkins)

2004 National Institutes of Health
"Targeting C-reactive protein in atherothrombotic disease"
$861,200 over 4 years

PUBLICATIONS

I. ORIGINAL PAPERS

A. Complement and induction of immunological responses

1. Pepys, M.B. (1972) Role of complement in induction of the allergic response. *Nature New Biol.*, **237:** 157-159.

2. Janossy, G., Humphrey, J.H., Pepys, M.B. and Greaves, M.F. (1973) Complement independence of stimulation of mouse splenic B lymphocytes by mitogens. *Nature New Biol.*, **245:** 108-112.

3. Pepys, M.B. (1974) Complement-mediated mixed aggregation of murine spleen cells. *Nature,* **249:** 51-53.

4. Feldmann, M. and Pepys, M.B. (1974) Role of C3 in *in vitro* lymphocyte cooperation. *Nature,* **249:** 159-161.

5. Pepys, M.B. and Taussig, M.J. (1974) Complement-independence of tolerance induction. *Eur. J. Immunol.*, **4:** 349-352.

6. Pepys, M.B. (1974) Role of complement in induction of antibody production *in vivo.* Effect of cobra factor and other C3-reactive agents on thymus-dependent and thymus-independent antibody responses. *J. Exp. Med.*, **140:** 126-145.

7. Pepys, M.B. and Butterworth, A.E. (1974) Inhibition by C3 fragments of C3-dependent rosette formation and antigen-induced lymphocyte transformation. *Clin. Exp. Immunol.*, **18:** 273-282.

8. Pepys, M.B. (1975) Studies *in vivo* of cobra factor and murine C3. *Immunology,* **28:** 369-377.

9. Pepys, M.B. and Wilson, D.V. (1975) A new immunoassay for C3. Application of the cell-linked antigen radioactive antibody (CLARA) technique. *J. Immunol. Methods,* **6:** 225-233.

10. Papamichail, M., Gutierrez, C., Embling, P., Johnson, P., Holborow, E.J. and Pepys, M.B. (1975) Complement dependence of localisation of aggregated IgG in germinal centres. *Scand. J. Immunol.*, **4:** 343-347.

11. Pepys, M.B., Bell, A.J. and Rowe, I.F. (1975) Sepharose-C3. I. Preparation and use as an immunosorbent. *Scand. J. Immunol.*, **5:** 75-78.

12. Pepys, M.B., Bell, A.J. and Rowe, I.F. (1975) Sepharose-C3. II. Specific depletion of complement receptor lymphocytes. *Scand. J. Immunol.*, **5:** 79-82.

13. Pepys, M.B. (1976) Role of complement in the induction of immunological responses. *Transplant Rev.*, **32:** 93-120.

14. Pepys, M.B., Wansbrough-Jones, M.H. and Mirjah, D.D. (1976) Suppression of IgA antibody produced by *in vivo* complement depletion. *Clin. Exp. Immunol.*, **23:** 378-381.

15. Pepys, M.B., Mirjah, D.D., Dash, A.C. and Wansbrough-Jones, M.H. (1976) Immunosuppression by cobra factor: distribution, antigen-induced blast transformation and trapping of lymphocytes during *in vivo* complement depletion. *Cell. Immunol.*, **21:** 327-336.

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B. C-reactive protein, amyloid P component and the acute phase response

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II. CHAPTERS, REVIEWS AND REPORTS

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IV. PATENT

1. Therapeutic and Diagnostic Agents for Amyloidosis. Freemedic PLC, M.B. Pepys and T.L. Blundell. US Patent No. 6,126,918 issued 3 October 2000.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of

PEPYS

Application No.: 09/737,544

Filed: December 18, 2000

Title: TREATMENT AND PREVENTION OF TISSUE DAMAGE

Group Art Unit: 1617

Confirmation No.: 1521

Examiner: Shengjun WANG

KATZ DECLARATION BY PROFESSOR MARK B. PEPYS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Mark B. Pepys, hereby declare as follows:

(1) I am Professor of Medicine and Head, Department of Medicine, Hampstead Campus, Royal Free and University College Medical School, London, U.K., and have worked in the field of chemical, biological, and clinical investigation of C-reactive protein (CRP) for 30 years.

(2) I am the sole inventor of U.S. Patent Application No. 09/737,544, entitled "Treatment and Prevention of Tissue Damage" ("the '544 application").

(3) I have invented a method for selecting a pharmaceutical for treating or preventing CRP-mediated tissue damage in a subject comprising identifying and selecting a compound that inhibits the binding of CRP to an autologous or extrinsic ligand thereof, and a method for treating or preventing C-reactive protein (CRP)-mediated tissue damage comprising administering to a subject in need thereof an effective amount of a compound capable of inhibiting the binding of CRP to an autologous or extrinsic ligand thereof. Original claims 1-25 and 39-48 of the '544 application that were elected for examination are directed to embodiments of my invention pertaining to a method for treating or preventing CRP-mediated tissue

damage a subject in need thereof comprising administering to the subject an effective amount of phosphocholine or a derivative thereof that inhibits the binding of CRP to an autologous or extrinsic ligand thereof.

(4) I have read and am familiar with the official action issued by the U.S. Patent and Trademark Office and dated September 2, 2005, in connection with the '544 application.

(5) I make this declaration in response to the official action issued September 2, 2005, in which claims 1-25 and 42-56 were rejected under 35 U.S.C. §103(a), because the claimed invention allegedly would have been obvious to a person of ordinary skill in the art at the time the invention was made, in view of Bhakdi et al. (Arterioscler. Thromb. Vasc. Biol., 1999, 19:2348-2354), in view of Griselli et al. (J. Exp. Med., December 20, 1999, 190(12): 1733-1739), further in view of Yedgar et al. (U.S. Patent No. 5,064,817) and Wissner et al. (U.S. Patent No. 4,640,913).

(6) I have reviewed the above-identified references cited by the examiner, *i.e.*, Bhakdi et al. (1999), Griselli et al. (1999), Yedgar et al. (U.S. Patent No. 5,064,817) and Wissner et al. (U.S. Patent No. 4,640,913).

(7) The Griselli et al. publication, of which I am a co-author, relates to the invention that is disclosed in the '544 application, and describes experimental results that are disclosed in the '544 application. For example, Figures 1 and 2 and Tables 1 and 2 of the Griselli et al. reference are identical to Figures 1 and 2 and Tables 2 and 3 of the '544 application.

(8) Pursuant to 37 C.F.R. §1.132, I hereby declare that I am the sole inventor of the subject matter disclosed in the Griselli et al. publication. The other authors of the publication, Massimo Griselli, Jeffrey Herbert, Winston L. Hutchinson, Kenneth M. Taylor, Muhammed Sohail, and Thomas Krausz, worked under my direction and supervision and were not co-inventors. *See* In re Katz, 215 U.S.P.Q. 14 (CCPA 1982).

At the time the work reported in the Griselli et al. article was performed, Massimo Griselli was an M.S. (Surgery) student, and I was his supervisor; Jeffrey Herbert was a clinical scientist (a member of staff in the department); Winston Hutchinson was a Principle Research Fellow (also member of staff in the dept); Professor Kenneth Taylor was joint supervisor of Massimo Griselli (Dept. of Surgery); and Muhammed Sohail and Thomas Krausz (both of whom are histopathologists) were acting as collaborators.

The work reported in the Griselli et al. reference was entirely my idea, including the experimental approach, all aspects of the experiments and the writing of the manuscript. I organized a suitable team including members of his own laboratory and others with the necessary expertise. Thus I enlisted the collaboration of K. Taylor, the Professor of Cardiac Surgery, who provided M. Griselli, a trainee surgeon, to do the rat surgery, and T. Krausz, the Professor of Histopathology, who provided M. Sohail, a trainee histopathologist, to do the histology. The other authors thus made essentially technical contributions, albeit at a high level, rather than intellectual contributions to the work.

(9) I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and may jeopardize the validity of the application or any patent issued thereon.

_____

MARK B. PEPYS

_____

Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of

PEPYS

Application No.: 09/737,544

Filed: December 18, 2000

Group Art Unit: 1617

Confirmation No.: 1521

Examiner: Shengjun WANG

Title: TREATMENT AND PREVENTION OF TISSUE DAMAGE

DECLARATION BY PROFESSOR MARK B. PEPYS PURSUANT TO 37 C.F.R. §1.131

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Mark B. Pepys, hereby declare as follows:

(1) I am Professor of Medicine and Head, Department of Medicine, Hampstead Campus, Royal Free and University College Medical School, London, U.K., and have worked in the field of chemical, biological, and clinical investigation of C-reactive protein (CRP) for 30 years.

(2) I am the sole inventor of U.S. Patent Application No. 09/737,544, entitled "Treatment and Prevention of Tissue Damage" ("the '544 application").

(3) I have invented a method for selecting a pharmaceutical for treating or preventing CRP-mediated tissue damage in a subject comprising identifying and selecting a compound that inhibits the binding of CRP to an autologous or extrinsic ligand thereof, and a method for treating or preventing C-reactive protein (CRP)-mediated tissue damage comprising administering to a subject in need thereof an effective amount of a compound capable of inhibiting the binding of CRP to an autologous or extrinsic ligand thereof. Original claims 1-25 and 39-48 of the '544 application that were elected for examination are directed to embodiments of my

invention pertaining to a method for treating or preventing CRP-mediated tissue damage in a subject in need thereof comprising administering to the subject an effective amount of phosphocholine or a derivative thereof that inhibits the binding of CRP to an autologous or extrinsic ligand thereof. Prior to my present invention, it was not known that CRP is capable of mediating tissue damage, or that a compound that inhibits the binding of CRP to an autologous or extrinsic ligand thereof such as phosphocholine or a derivative thereof could be administered to a subject to successfully treat or prevent CRP-mediated tissue damage.

(4) I have read and am familiar with the official action issued by the U.S. Patent and Trademark Office dated September 2, 2005, in connection with the '544 application.

(5) I make this declaration in response to the official action issued September 2, 2005, in which claims 1-25 and 42-56 were rejected under 35 U.S.C. §103(a), because the claimed invention allegedly would have been obvious to a person of ordinary skill in the art at the time the invention was made, in view of Yeh et al. (U.S. Patent No. 6,764,826), in view of Bhakdi et al. (Arterioscler. Thromb. Vasc. Biol., 1999, 19:2348-2354), and further in view of Yedgar et al. (U.S. Patent No. 5,064,817) and Wissner et al. (U.S. Patent No. 4,640,913).

(6) I have reviewed the above-identified references cited by the examiner, *i.e.*, Yeh et al. (U.S. Patent No. 6,764,826), Bhakdi et al. (1999), Yedgar et al. (U.S. Patent No. 5,064,817) and Wissner et al. (U.S. Patent No. 4,640,913).

(7) The effective date of U.S. Patent No. 6,764,826 of Yeh et al., which is cited as the primary reference in the rejection of claims 1-25 and 42-56 under 35 U.S.C. §103(a), is June 8, 2000, which is the date that the patent is effective as a 102(e) reference (*see* 37 C.F.R. §1.131(a)(1)). The effective date of U.S. Patent No. 6,764,826 of Yeh et al. is therefore less than a year prior to the filing date of the present application, which was filed on December 18, 2000.

(8) The six claims of U.S. Patent No. 6,764,826 of Yeh et al. are all directed to an in vitro method for screening for modulators of human C-reactive protein. The claims of U.S. Patent No. 6,764,826 of Yeh et al. are therefore directed to subject matter that is different from the subject matter of the rejected claims, which are directed to a therapeutic method for treating or preventing CRP-mediated tissue damage in a subject.

(9) I hereby declare that I invented the subject matter of the rejected claims prior to the effective date of U.S. Patent No. 6,764,826 of Yeh et al., which is June 8, 2000. Evidence of my prior invention is found in Griselli et al., a scientific article published in the Journal of Experimental Medicine (vol. 190 (sec. 12), pages 1733-1739) with a publication date of December 20, 1999. As I declared in a declaration under 37 C.F.R. §1.132 submitted herewith, I am the sole inventor of the subject matter disclosed Griselli et al., as the other authors of the publication worked under my direction and supervision and were not co-inventors. Griselli et al. provides the first publicly disclosed demonstration that CRP is capable of mediating tissue damage in a mammal. The materials and methods, experimental results shown in Figures 1-2 and Tables I-II, and the discussion of the significance of these results with respect to clinical benefits provided by to patients treating or preventing CRP-mediated tissue damage associated with traumatic, infectious, inflammatory, and neoplastic tissue-damaging conditions, described on pages 1734-1737 of Griselli et al., are identical to materials and methods, experimental results, and discussion, found on pages 25-34, 36, and 37 of the application filed on December 18, 2000. After the publication of Griselli et al. on December 20, 1999, the inventor has worked diligently on the claimed invention, as evidenced by the filing of the present application, the publication of Gill et al. in 2004 (Journal of Cerebral Blood Flow and Metabolism, 24(11:1214-1218)), which describes experimental results demonstrating that CRP-mediates tissue damage associated with cerebral infarct, and the award to the inventor in 2004 by the U.S. National Institutes of Health of a research grant of $861,200 over 4 years entitled "*Targeting C-reactive protein in atherothrombotic disease.*"

(10) I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and may jeopardize the validity of the application or any patent issued thereon.

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MARK B. PEPYS

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Date